Metabolic fate and function of dietary glutamate in the gut[1–5]

Douglas G Burrin and Barbara Stoll

ABSTRACT

Glutamate is a main constituent of dietary protein and is also consumed in many prepared foods as an additive in the form of monosodium glutamate. Evidence from human and animal studies indicates that glutamate is a major oxidative fuel for the gut and that dietary glutamate is extensively metabolized in first pass by the intestine. Glutamate also is an important precursor for bioactive molecules, including glutathione, and functions as a key neurotransmitter. The dominant role of glutamate as an oxidative fuel may have therapeutic potential for improving function of the infant gut, which exhibits a high rate of epithelial cell turnover. Our recent studies in infant pigs show that when glutamate is fed at higher (4-fold) than normal dietary quantities, most glutamate molecules are either oxidized or metabolized by the mucosa into other nonessential amino acids. Glutamate is not considered to be a dietary essential, but recent studies suggest that the level of glutamate in the diet can affect the oxidation of some essential amino acids, namely leucine. Given that substantial oxidation of leucine occurs in the gut, ongoing studies are investigating whether dietary glutamate affects the oxidation of leucine in the intestinal epithelial cells. Our studies also suggest that at high dietary intakes, free glutamate may be absorbed by the stomach as well as the small intestine, thus implicating the gastric mucosa in the metabolism of dietary glutamate. Glutamate is a key excitatory amino acid, and metabolism and neural sensing of dietary glutamate in the developing gastric mucosa, which is poorly developed in premature infants, may play a functional role in gastric emptying. These and other recent reports raise the question as to the metabolic role of glutamate in gastric function. The physiologic significance of glutamate as an oxidative fuel and its potential role in gastric function during infancy are discussed. *Am J Clin Nutr* 2009;90(suppl):850S–6S.

INTRODUCTION

Glutamate is a major oxidative fuel for the intestine. In addition, glutamate is an important precursor for other biologically active molecules, including glutathione, proline, and arginine (1) (**Figure 1**). Several studies have shown that glutamate is extensively metabolized by the intestine. Seminal studies by Windmueller and Spaeth (2, 3) with the use of an in situ rat intestine established that only small fractions of luminally administered glutamate are absorbed into the mesenteric venous blood. Subsequent studies in young pigs, preterm infants, and adult humans have confirmed that dietary glutamate is extensively metabolized by the intestine and that oxidation to carbon dioxide is a major metabolic fate (4–7). Our recent studies in young pigs also indicate that enteral glutamate is extensively oxidized even when the dietary intake fed is 3- to 4-fold higher than normal (8).

Molecular evidence is growing that glutamate functions as a signaling molecule in the enteric nervous system and modulates neuroendocrine reflexes in conjunction with the umami taste (9) and nutrient sensing in the gastrointestinal tract (10). Glutamate is the main excitatory neurotransmitter in the body, and multiple glutamate receptors and transporters have been found in the gastrointestinal tract and enteric nervous system (11–13). Recent studies also have shown that the 2 vesicular glutamate transporters (VGLUTs), VGLUT1 and VGLUT2, are present both in enteric nervous system and pancreatic tissue (14, 15).

The central importance of glutamate as a major gut oxidative fuel and key enteric neurotransmitter may have therapeutic potential for improving neonatal gut function. The premature neonatal intestine exhibits a high rate of epithelial growth and cell turnover, but poorly developed gastroduodenal function limits the ability to provide critically important enteral nutrition (16, 17). However, the use of glutamate as an enteral supplement to augment neonatal gut function must be balanced against the consideration that high doses of glutamate can induce neurotoxicity (18, 19). This article reviews the literature on intestinal glutamate metabolism in the developing gut, mainly the small intestine, and discusses the potential significance of recent findings from a functional, nutritional, and clinical perspective.

MAJOR GUT OXIDATIVE FUEL

It is now well established that the splanchnic bed derives most of its energy from the catabolism of amino acids, rather than glucose or fatty acids. The liver has been historically considered the main site of amino acid catabolism and oxidation. However,

[1] From the US Department of Agriculture, Agricultural Research Service, Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX.

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[5] Address correspondence to DG Burrin, Children's Nutrition Research Center, 1100 Bates Street, Houston, TX 77030. E-mail: dburrin@bcm.tmc.edu.

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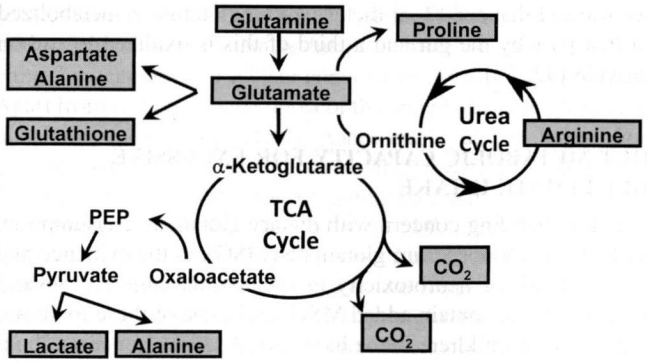

FIGURE 1. Metabolic fates of dietary glutamate in the intestine. Glutamate is an important metabolic link between the tricarboxylic acid (TCA) cycle and urea cycle involved in cellular energy generation and nitrogen disposal. PEP, phosphoenolpyruvate.

since the classic studies of Windmueller and Spaeth (2, 3, 20–22), it has become apparent that the gut, particularly the intestine, also is a major site of catabolism of several amino acids, mainly nonessential amino acids glutamine, glutamate, and aspartate. An important distinction to be made, however, is that, although amino acids are catabolized in both the liver and gut tissues, the extent to which they are completely oxidized to carbon dioxide varies. Jungas et al (23) systematically reviewed the metabolic fate of dietary amino acids in the gut, liver, kidney, and muscle and derived 2 important conclusions. First, they estimated that a primary metabolic fate of amino acid carbon in the liver is conversion to glucose. They argued that sufficient ATP is generated from the partial oxidation of dietary amino acids to generate roughly half of the liver's energy needs, an amount that approximates the energy required for the synthesis of glucose. Thus, although amino acids are consumed in oxidative metabolic pathways in the liver, the complete oxidation of amino acids would far exceed the liver's energy needs and capacity to handle the end products. A second important observation from their analysis was that the hepatic metabolism of amino acids to glucose makes nearly two-thirds of the total energy content of dietary amino acids available to peripheral tissues (as glucose). As a result, there is no need for peripheral tissues to synthesize a complex array of enzymes to oxidize amino acids and synthesize urea. Glutamate is a key amino acid linking hepatic amino acid catabolism and gluconeogenesis, because many amino acids are first catabolized to glutamate by transamination (24).

The seminal studies of Windmueller and Spaeth (2, 3, 20–22) were first to show evidence of extensive metabolism of glutamine, glutamate, and aspartate in in situ intestinal perfusions in anesthetized rats deprived of food. Results from young piglets fed a high-protein, milk-based formula indicated that >95% of the dietary glutamine, glutamate, and aspartate are used in vivo by the gastrointestinal tract (1, 4). The studies of Windmueller and Spaeth (2, 3, 20–22) focused attention on the role of glutamine as the main oxidative fuel in the gut. However, note that both glutamate and aspartate are of perhaps equal importance as intestinal oxidative fuels. Recent studies in young pigs and humans confirm the extensive intestinal oxidation of dietary ^{13}C-labeled glutamate, glutamine, and aspartate (4–7, 25, 26).

The intestinal metabolism of glutamate is presumed to occur largely in epithelial cells lining the mucosa, namely enterocytes. The first step in epithelial glutamate metabolism is transport from the intestinal lumen across the apical membrane. Glutamate transport by the enterocyte apical membrane occurs mainly by the high-affinity X^-_{AG} system and to a lesser extent by the low-affinity B^o system; the X^-_{AG} system transports both glutamate and aspartate. The molecular identities of 4 proteins capable of X^-_{AG} system activity have been described in various tissues, including glutamate-aspartate transporter 1 (GLAST-1), glutamate transporter 1 (GLT-1), excitatory amino acid carrier 1 (EAAC-1), and excitatory amino acid transporters 4 and 5 (12, 13, 27, 28). Studies with pig and rodent tissues show that EAAC-1 is the most abundant glutamate transporter in the intestine and is expressed on the apical, brush border membrane throughout the small intestine. We found the expression of EAAC-1 in isolated epithelial cells all along the villus and crypt, and this has been supported by immunohistochemical analysis showing expression in the brush border membrane (12, 13). The latter study reported that EAAC-1 expression was localized mainly to the small intestine and was not highly expressed in the stomach or large intestine. However, both the GLAST and GLT-1 transporters were expressed in various cell compartments within the stomach and to a lesser extent in the small intestine.

Once inside the intestinal enterocyte, glutamate catabolism occurs in the cytosol and mitochondria by transamination by aspartate aminotransferase, alanine aminotransferase, branched-chain aminotransferase, and glutamate dehydrogenase (GDH) enzymes, all of which are present in the stomach, small intestine, and colon (29–31) (**Figure 2**). Interestingly, the activity of GDH is increased approximately 3-fold in the small intestine after weaning in piglets and rats (32, 33). The resulting keto-acid product of branched-chain aminotransferase and GDH is α-ketoglutarate, which can then enter the tricarboxylic acid cycle and be metabolized, yielding carbon dioxide. The in situ studies with perfused rat intestine and those in vivo with piglets and humans indicate that most of the glutamine (55–70%), glutamate (52–64%), and aspartate (52%) are oxidized to carbon

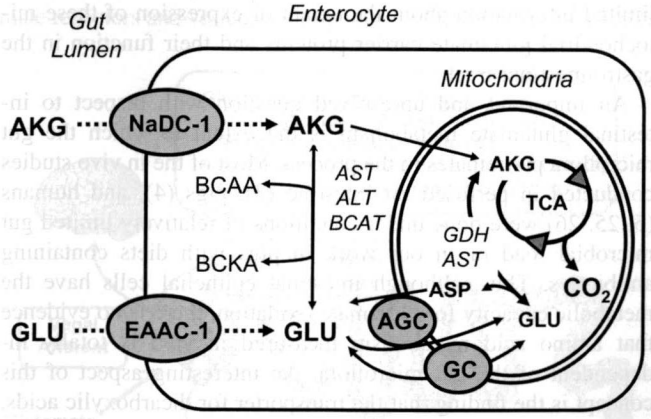

FIGURE 2. Metabolic fate of dietary glutamate (GLU) and α-ketoglutarate (AKG) in the intestinal enterocyte. Dietary GLU and AKG are transported from the gut lumen into the enterocyte by the excitatory amino acid carrier-1 (EAAC-1) and Na-dicarboxylate cotransporter-1 (NaDC-1) transporters, respectively. Within the enterocyte, both GLU and AKG can undergo transamination and transport into the mitochondria for oxidative metabolism to CO_2. BCAA, branched-chain amino acid; BCKA, branched-chain keto acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BCAT, branched-chain aminotransferase; TCA, tricarboxylic acid; GDH, glutamate dehydrogenase; AGC, aspartate-glutamate carrier; GC, glutamate carrier.

dioxide (2, 4, 20, 22). Note that, although there is extensive uptake and metabolism of these 3 amino acids, their carbon skeletons are not completely oxidized to carbon dioxide, and they do not account for all of the carbon dioxide released by the gut. The remaining carbon atoms from these 3 substrates that are not oxidized to carbon dioxide are converted to lactate, alanine, proline, citrulline, ornithine, and arginine and then released into the portal circulation (2, 4, 20). The metabolic fate of nitrogen from these amino acids is not fully understood. However, evidence suggests that a portion of the nitrogen derived from glutamine and glutamate metabolism is transferred to ammonia and other amino acids, including citrulline, ornithine, proline, and arginine; much of the nitrogen from these products is converted to urea in the liver.

Surprisingly few reports of glutamate oxidation measured in isolated intestinal epithelial cells are available, in contrast to that of glutamine and glucose, which highlights the perception that glutamine and glucose are the main gut oxidative fuels (34–36). Indeed, studies with isolated enterocytes show that glutamine and glucose are important intestinal oxidative fuels (37–39). Glutamine also effectively suppresses glucose oxidation in enterocytes, whereas glucose has little effect on glutamine oxidation. The oxidation of glutamine and its suppression of glucose oxidation was also found to be nearly twice as high (60%) in the proximal than in the distal (31%) small intestine (38). The relation is consistent with in vivo studies in piglets, showing that, although glucose represents an important oxidative fuel (29%), the proportion of glucose oxidized completely to carbon dioxide is substantially less than that of either glutamate or glutamine. The implication is that glutamine and glutamate are preferentially channeled toward mitochondrial oxidation, whereas most of the glucose is used for other metabolic or biosynthetic purposes. Mitochondrial oxidation of glutamate by intestinal epithelial cells involves mitochondrial transport via recently identified glutamate carrier proteins. These glutamate and aspartate-glutamate carrier proteins act as mitochondrial antiporters for either protons or aspartate, respectively, from the mitochondria (40). There is limited information about the extent of expression of these mitochondrial glutamate carrier proteins and their function in the gastrointestinal tract.

An important and unresolved question with respect to intestinal glutamate metabolism is the extent to which the gut microflora participates in the process. Most of the in vivo studies conducted in perfused rat intestine (3), pigs (4), and humans (5, 25, 26) were done under conditions of relatively limited gut microbial load or in our work in pigs with diets containing antibiotics. Thus, although intestinal epithelial cells have the metabolic capacity for glutamate oxidation, there is no evidence that amino acid metabolism measured in vivo is totally independent of the gut microflora. An interesting aspect of this concept is the finding that the transporter for dicarboxylic acids, specifically α-ketoglutarate, is present in pig gastrointestinal tissues, including stomach, small intestine, and large intestine (41). The teleologic explanation for the expression of this dicarboxylic acid transporter in the gut mucosa is intriguing and raises the question as to whether glutamate is catabolized to α-ketoglutarate by gut microbes and taken up by intestinal epithelial cells and further metabolized. In this respect, we have found that α-ketoglutarate, like glutamate, is extensively metabolized by the gastrointestinal tract when fed enterally to pigs; we showed that ≈80% of dietary α-ketoglutarate is metabolized in first pass by the gut and a third of this is oxidized to carbon dioxide (42, 43).

GUT METABOLIC CAPACITY FOR EXCESSIVE GLUTAMATE INTAKE

A longstanding concern with dietary glutamate consumption, particularly monosodium glutamate (MSG), is the evidence and potential risk of neurotoxicity in infants and children. Several prepared foods contain added MSG, and some of these foods are consumed by children. Some have raised serious concerns about the potential risk of dietary MSG, parenteral glutamate, and its implications for human diseases, such as obesity (44–46). However, it is critically important to recognize that the evidence of neurotoxicity in several experimental models only occurred with extremely high enteral and parenteral glutamate loads (19, 47, 48). Note that the amount of glutamate given in the study by Hermanussen et al (44) with pregnant rats was 2.5 and 5 g MSG/d. Assuming that the rats consumed all the MSG given to them, this translates into nearly 10–20 g/kg body weight of glutamate. For perspective, the average breastfed or formula-fed infant receives a daily glutamate intake of <1 g/kg. Moreover, a recent study in preterm infants observed no change in plasma glutamate concentration after supplementation of formula with $\leq$4-fold normal glutamate intake (49). Several reviews have concluded that there is no evidence linking MSG to long-term serious health problems in the general population; thus, MSG is generally recognized as a safe food additive (50).

An important factor in the consideration of dietary glutamate or MSG toxicity is the extent of absorption into the circulation. Several studies indicate that under normal dietary conditions most of the dietary glutamate is either metabolized or oxidized to carbon dioxide by the gut in first pass. However, the capacity of the gut, mainly the small intestine, to metabolize dietary glutamate when ingested in excess was unknown. Thus, to test this question, we nvestigated the extent of gastrointestinal tissue glutamate metabolism in young pigs fed supraphysiologic intakes of glutamate (8). Note that these measurements we made with the use of portal balance represent metabolism of all gastrointestinal tissues, including the stomach, small intestine, and large intestine. However, it is presumed that much of the metabolism represents first-pass metabolism by the small intestinal mucosal epithelial cells. We quantified the metabolic fate of dietary [^{13}C]-glutamate in young pigs when administered intraduodenally with a normal milk formula, control diet ($\approx$600 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}) or diet supplemented with MSG $\leq$400% of the control glutamate intake. We found that across the wide range of glutamate intakes (600–2100 μmol $\cdot$ kg^{-1} $\cdot$ h^{-1}) the fractional percentage of glutamate absorption was not significantly different (13–17% dietary intake). However, the absolute rate of dietary glutamate absorption and the circulating plasma concentration did increase significantly. When we compared the gut metabolism of [^{13}C]-glutamate, we found that oxidation to $^{13}CO_2$ was a major fate, yet was lower (33% compared with 49%) in pigs fed 350% compared with 100% glutamate intake, respectively.

The findings from this recent study have shown that the gastrointestinal tract capacity for metabolism of dietary glutamate is substantial, even when the intake is in excess of the

normal amount. When the dietary intake is increased 3–4-fold, most of the dietary glutamate intake is metabolized by the gut, either for generation of ATP or conversion into other amino acids. Apart from carbon dioxide, most of the end products of glutamate metabolism were predictably nonessential amino acids. For example, when the dietary glutamate intake was increased 3-fold, the net intestinal production of glutamine, aspartate, and ornithine increased significantly by 4.8-, 4.0-, and 2.7-fold, respectively. The intestinal absorption of other amino acids also tended to increase in pigs fed excessive loads (300% level) of dietary glutamate, including proline, arginine, and branched-chain amino acids (BCAAs). We would expect to see increased intestinal production of proline and arginine under excessive dietary glutamate intakes because these are byproducts of glutamate metabolism by pyrroline-5-carboxylate. In contrast, there was a surprising trend for increased net BCAA absorption. This observation supports another recent study in which we observed a 50% increase in net intestinal leucine absorption in pigs fed supplemental α-ketoglutarate (42). Taken together, these findings suggest that under conditions of increased dietary availability of key gut oxidative substrates, namely glutamate and α-ketoglutarate, gut metabolism of BCAAs appeared to be reduced or spared. This possibility is intriguing, given the evidence in vivo and in vitro that BCAAs are extensively oxidized by the intestine to carbon dioxide (51–53). Moreover, glutamate and α-ketoglutarate are transamination partners in the reversible reaction catalyzed by BCAA transaminase. The relation between dietary glutamate intake and essential amino acid oxidation in the gastrointestinal tract is currently being investigated in our laboratory.

GASTRIC GLUTAMATE METABOLISM

Glutamate, like other constituent amino acids ingested in dietary protein, is normally absorbed and metabolized in the small intestine subsequent to proteolytic digestion. However, some amino acids, especially dietary MSG, are ingested in a free form and thus may be metabolized differently when they are presented to the epithelial mucosa of the stomach. To test this, we compared the metabolic fate of dietary [^{13}C]-glutamate in young pigs when administered the same control diet and supplemental glutamate intakes by the intragastric and intraduodenal feeding route (8). The latter route occasionally occurs in infants fed by transpyloric catheter or jejunostomy. Similar to the intraduodenal feeding route, we found that oxidation to $^{13}CO_2$ was the major metabolic fate (35–42%) of intragastric [^{13}C]-glutamate. However, in contrast to intraduodenal feeding (range: 13–17%), the fractional rate of gastrointestinal glutamate absorption when given intragastrically was significantly higher (range: 17–28%) in pigs fed 100% compared with 300%, respectively. We compared the relation between net intestinal glutamate absorption and dietary glutamate intake in pigs fed by either the intragastric or intraduodenal route (**Figure 3**). Our results suggest that the rate of dietary glutamate absorption is higher when feeding occurs by the intragastric route, but only when glutamate is fed in excess of the normal dietary intake in the free form.

Our observation of increased gut glutamate absorption during intragastric or intraduodenal feeding may suggest the possible capacity for glutamate transport by the stomach mucosa. Further

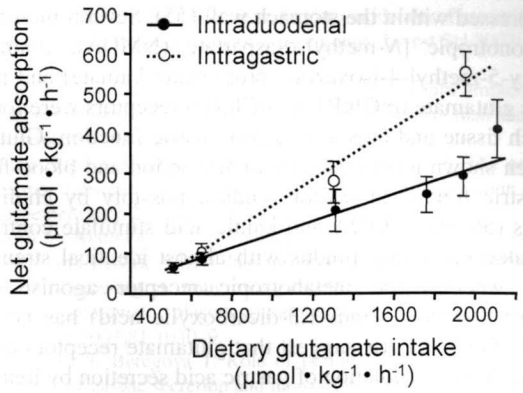

FIGURE 3. Mean (±SD) rates of gastrointestinal glutamate absorption as a function of increasing dietary glutamate intake measured in infant piglets. The rate of dietary glutamate absorption was greater when administered by the intragastric route than by the intraduodenal route. Reproduced with permission from reference 8.

studies are needed to measure this directly with the use of preparations in which luminal glutamate absorption is quantified when the pylorus is ligated to prevent passage into the small intestine. The direct evidence for amino acid transport and absorption across the gastric mucosa is limited, although several amino acid transporters are expressed in gastric epithelial cells, including some involved in glutamate transport (13, 54). Gastric glutamate transport and absorption may be physiologically significant in dietary circumstances that involve feeding free amino acid–based diets, which occurs clinically with some hypoallergenic formulas fed to infants and children.

GLUTAMATE AND GASTRIC FUNCTION

Apart from the potential capacity for glutamate transport into the blood, the stomach is also emerging as an important site of glutamate sensing and glutamate-mediated signaling of digestive function (**Figure 4**). In addition to membrane transporters (EAAC-1, GLAST, and GLT-1), several other classes of glutamate receptors and vesicular transporters (VGLUT1 and VGLUT2)

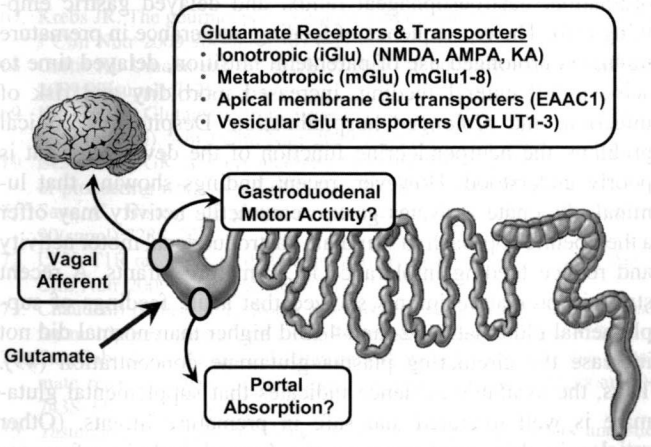

FIGURE 4. Physiologic and metabolic functions of glutamate within the stomach. Glutamate sensing and metabolism may be mediated by several groups of glutamate receptors and transporters expressed with the mucosal epithelium and enteric nervous system. iGlu, ionotropic glutamate; mGlu, metabotropic glutamate; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; KA, kainate; EAAC1, excitatory amino acid carrier-1; VGLUT1–3, vesicular glutamate transporter-1 to -3.

are expressed within the stomach wall (55). Several members of both ionotropic [*N*-methyl-D-aspartate (NMDA); α-amino-3-hydroxy-5-methyl-4-isoxazole, propionate; kainate] and metabotropic glutamate (mGluR1 to mGluR8) receptors were found in stomach tissue and appear to affect gastric function. Glutamate has been shown to activate contractile action and blood flow in the gastric fundus in several studies, possibly by cholinergic neurons (56–60). NMDA and kainic acid stimulate contraction of isolated rat gastric fundus with almost identical strength of action, whereas the metabotropic receptor agonist ACPD (aminocyclopentane-*trans*-1,3-dicarboxylic acid) has no effect (59–62). Other reports suggest that glutamate receptors also are involved in the modulation of gastric acid secretion by ionotropic receptors, and aspartate regulates acid secretion in the stomach by inhibiting histamine release through the NMDA receptors. NMDA receptor-mediated modulation of gastric motor function also may accelerate gastric emptying and food intake. An antagonist of NMDA receptors, MK-801 (dizocilpine), increased meal size and duration in rats, but it did not increase sham feeding or attenuate reduction of sham feeding by intraintestinal nutrient infusions (63). Another report has shown that ionotropic receptors are involved in mechanosensitive vagal responses in the gastric antrum (58). Studies show that intragastric glutamate infusion specifically stimulates afferent gastric vagal nerves, whereas all other amino acids had no effect (10, 64). Moreover, the activation of vagal afferent activity was dose dependent and effective within the physiologic range of normal dietary glutamate intakes. The mechanism whereby free luminal glutamate is sensed by the gastric mucosa appears to involve serotonin and nitric oxide production and release. This group showed the expression of the mGluR1 in the rat gastric fundus (65). These studies suggest that neural sensing of gastric luminal glutamate may play a direct role in controlling digestion function.

CLINICAL APPLICATION IN INFANTS

Premature infants frequently present with significant gastroduodenal motor dysfunction, which is manifest clinically as feeding intolerance resulting from delayed suck-swallow coordination, gastroesophageal reflux, and delayed gastric emptying (16). The consequence of feeding intolerance in premature infants is prolonged use of parenteral nutrition, delayed time to achieve full enteral feeding, increased morbidity and risk of infection, and prolonged hospitalization. Despite this clinical problem, the neuroendocrine function of the developing gut is poorly understood. However, recent findings showing that luminal glutamate activates gastric contractile activity may offer a therapeutic approach to stimulate gastroduodenal motor activity and reduce feeding intolerance in premature infants. A recent study in premature infants showed that acute feedings of supplemental glutamate at 2- and 4-fold higher than normal did not increase the circulating plasma glutamate concentration (49). Thus, the available evidence indicates that supplemental glutamate is well tolerated and safe in premature infants. (Other articles in this supplement to the Journal include references 66–94.)

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